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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,594	01/05/2006	Alain Prochiantz	275010US0XPCT	1972

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
05/30/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/541,594	PROCHIANTZ ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 10-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/15/05; 8/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 7-9, in the reply filed on 2/14/2008 is acknowledged.

Claims 1-6 and 10-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/14/2008.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Schutze-Redelmeier et al (1996, J. Immunol.) as evidenced by Derossi et al (1998, cited by applicants).

Schutze-Redelmeier et al teach the antennapedia homeodomain (AntpHD), in particular its third helix, can be used to translocate peptides and oligonucleotides into cells (abstract, and ¶ linking pages 650-651). Various fusion proteins of the AntpHD to peptides (a macromolecular "cargo") were prepared (Fig. 1). Absent evidence to the contrary, such peptides are less than 1 μm: for example, a small virus such as polio is only 20 nm across its largest dimension (and typical human cells average 10-30 μm in diameter). The "cargos" attached to the AntpHD comprised hydrophobic domains: 1) the SIV tag of the 2.3.5 fusion protein comprised I, P (two

residues),G, and L (three residues), all hydrophobic amino acids; 2) the c-myc tag (e.g. R3 and R4 proteins) comprised K, L (two residues), I, and S, all hydrophobic residues; 3) the 147-155 influenza NP peptide of the 2.3.5 construct comprised T (two residues), Y, R (two residues), A, L, and V, all hydrophobic residues (all sequences found within the legend of Figure 1). Upon transduction into cells, the c-myc tag and influenza NP peptide within the fusion proteins were detected immunologically, thus they were present on the "surface", i.e. they comprised epitopes that were recognized by other proteins (immunoglobulins or T cell receptors, see page 652, first column, first full ¶ to second column, first full ¶, and Fig. 2). The AntpHD inherently comprises a third helix, responsible for transduction, that does not comprise a Trp-Trp pair (see Figure 1 of Derossi et al), and thus is within the scope of claim 7. Regarding claim 8, a review of the Sequence Listing reveals SEQ ID NO: 2 to be a 16-mer peptide that requires only a tryptophan (W) at position 6. This is because the Sequence Listing states that "Xaa" at positions 1-5 and 7-16 "can be any naturally occurring amino acid". The AntpHD third helix (residues 43-58 in Figure 1 of Derossi et al) comprises such a 16-mer. The fusion proteins of Schutze-Redelmeier et al were injected into mice in saline or adjuvants (page 653, second column, first full ¶), both considered to be pharmaceutical compositions as required by claim 9.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising transducing peptides known in the prior art, does not reasonably provide enablement for compositions comprising the broad genus of transducing peptides encompassed by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art, Scope of the invention, and State of the art. The art concerning predicting novel, functional transducing peptides is unpredictable. In a review published in 2004, Joliot et al (Nat. Cell Biol., Vol. 6: pp. 189-196) teach that whereas many such peptides were known (e.g. Table 1), modification of such peptides by even single amino acid changes disrupts transducing capability (page 193, third column, first full ¶), indicating that transduction is not a property of all peptides. The minimum sequence required for many of the known transducing peptides to retain function was also unknown (page 194, beginning of the first column). Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its

tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976) discloses that even for peptide hormones, which are small proteins similar to many of the claimed transducing peptides, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary derivatives with the transducing activity of, for example the known penetratin peptide used in the instant application, since the amino acid sequence of such polypeptides could not be predicted - even were the activity known.

The claims are broad in nature and read on using any peptide sequence less than 16 or more than 30 residues without any upper limit (claim 7), or in the case of claim 8, any peptide comprising at least a 16-mer with a tryptophan at position 6 (i.e. SEQ ID NO: 2, see the explanation of the breadth of SEQ ID NO: 2 explained above). Thus, the claims encompass using, for example, a 10-mer of alanine, glycine, etc. which are not known to transduce "cargo", and could not be predicted to do so for reasons set forth above. To put the situation in perspective, the number of possible amino acid sequences of 15 amino acids in length is 20^{15} (approx. 3×10^{19}), and of 40 amino acids in length is 20^{40} (approx. 10^{51}), all of which are encompassed by the instant claims. The recitation of SEQ ID NO: 2 in claim 8 is of little help, as SEQ ID NO: 2 can be viewed as a random 15-mer with a fixed W residue at position 6, and thus encompasses all the permutations set forth above (i.e. 20^{15} possible sequences) and additional

possible sequences due to the "comprising" language used in claim 8. Neither the specification nor the prior art teach how to make and test all of the possible sequences set forth above such that they would be commensurate in scope with the claims, i.e. act as a transducing peptide.

Thus, the state of the art regarding the production and use of transducing peptides other than those already taught in the prior art, is poorly developed and unpredictable. The development of such transducing peptides would have to be done empirically.

Number of working examples. Applicants have provided a working example of using a known transducing peptide, penetratin (the third helix of AntpHD).

Amount of guidance. Applicants provide no direction or guidance regarding modifications of known transducing peptides that function as claimed. The specification requires the skilled artisan to practice trial and error experimentation with a vast genus of possible peptides in order to determine which will function as claimed.

Nature of the invention. The invention involves the unpredictable art of making and using transducing peptides.

Level of skill in the art. While the level of skill in the art of using known transducing peptides to transduce macromolecular cargo is high, the level of skill in the art of making and using unknown transducing peptides to transduce macromolecular cargo is low. The unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and

excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The instant abstract uses the legal phraseology "said".

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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